$TiCl_4$-catalyzed synthesis of peroxyacetals from aldehydes

Chen-Yu Tsai, Lu-An Chen, and Kuangsen Sung

Abstract: Peroxyacetals **2a**–**2j** were prepared by $TiCl_4$-promoted nucleophilic addition of both *tert*-butyl hydroperoxide (TBHP) and an alcohol to the corresponding aldehyde. The reaction works well with a variety of aldehydes, but not with ketones. The magnitude of the equilibrium constant for hemiacetal formation plays an important role; a large constant enables high conversion to peroxyacetal.

Key words: peroxyaceta , aldehyde, titanium chloride, peroxide.

Résumé : On a préparé les peroxyacétals **2a**–**2j** par addition nucléophile catalysée par le $TiCl_4$ simultanée de l'hydroperoxyde de *tert*-butyle et d'un alcool sur l'aldéhyde correspondant. La réaction fonctionne bien avec un grand nombre d'aldéhydes, mais elle ne donne pas de bons résultats avec les cétones. La valeur de la constante d'équilibre de formation de l'hémiacétal joue un rôle important; avec une constante dont la valeur est élevée, on obtient un degré élevé de conversion en peroxyacétal.

Mots-clés : peroxyacétal, aldéhyde, chlorure de titane, peroxyde.

[Traduit par la Rédaction]

Introduction

The number of reported peroxide natural products continues to increase and some organic peroxides have been discovered to have antimalarial properties,[1] therefore, peroxide synthesis has been studied for a long time and is of continuing interest for chemists.[2–4,5,6] In last two decades, peroxyacetals have been used as substrates in the development of new methodology for peroxide synthesis. For example, neighboring iodo, alkoxy, acetoxy, and silyl groups impart useful levels of diastereoselection in the Lewis acid-mediated allylation of peroxyacetals, generating chiral peroxides.[2] Peroxyacetals undergo reaction with allyltrimethylsilane, silyl enol ethers, and silyl ketene acetals in the presence of Lewis acids, such as $TiCl_4$, $SnCl_4$, and trimethylsilyl triflate, to afford homoallyl peroxides, 3-peroxyketones, and 3-peroxyalkanoates, respectively.[3] Acid hydrolysis of peroxyacetals may generate alkyl hydroperoxides.[4] Hence, the synthesis of peroxyacetals has become interesting as well.

The major synthetic route to monoperoxyacetals or bisperoxyacetals is through the ozonolysis of alkenes or enol ethers, followed by alkylation or silylation of the resulting hydroperoxyacetals.[1c,4,7] The drawback of this general synthetic method is that the selectivity of ozonolysis is poor and cannot be used for substrates containing ozone-sensitive groups. Bisperoxyacetals and (or) ketals can be synthesized by another method, which involves the reaction of acetals or ketals with H_2O_2 in the presence of protic or Lewis acids, such as $BF_3{\cdot}OEt_2$, HCl, AcOH, and tungstic acid, followed by alkylation or silylation of the resulting dihydroperoxyacetals.[8] Bisperoxyacetals or ketals can also be directly synthesized by the reaction of acetals or ketals with alkyl hydroperoxides in the presence of protic or Lewis acids ($BF_3{\cdot}OEt_2$).[5] Recently, a newly developed methodology for monoperoxyacetals or bisperoxyacetals used iodine as a catalyst to peroxidize carbonyl compounds and, in this method, both ketones and aldehydes have the possibility of being converted into bisperoxyacetals or ketals or monoperoxyacetals or ketals.[6] In this paper, we will introduce a novel synthetic method that uses $TiCl_4$ as a catalyst and selectively converts an aldehyde into monoperoxyacetals. For this methodology, it is unnecessary to convert aldehydes into acetals or vinyl ethers before the preparation of peroxyacetals. In addition, this method for peroxyacetal synthesis works only for aldehydes, not for ketones, and that is quite different from ketal synthesis. To figure out what causes the difference, we propose a reaction mechanism for the $TiCl_4$-promoted peroxyacetal synthesis. A detailed analysis will lead us to the answer.

Results and discussion

In this paper, we found that reaction of an aldehyde with 1 equiv of alcohol and 1.7 equiv of TBHP in the presence of a catalytic amount of $TiCl_4$ (0.1 equiv) in $CDCl_3$ solvent generated a peroxyacetal. To understand the scope of this reaction, we tested various aldehydes and alcohols for this type of reaction, and the results are shown in Table 1. First, we used an aromatic aldehyde (benzaldehyde) as an aldehyde substrate to react with a primary alcohol (*n*-BuOH), secondary alcohol (*i*-PrOH), benzyl alcohol, or tertiary alcohol (*t*-BuOH) for the peroxyacetal synthesis. What we found was that they

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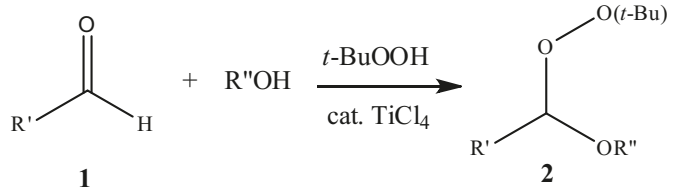
C.-Y. Tsai, L.-A. Chen, and K. Sung. Department of Chemistry, National Cheng Kung University, Tainan, Taiwan.

Corresponding author: K. Sung (kssung@mail.ncku.edu.tw)

Table 1. $TiCl_4$-promoted synthesis of the peroxyacetals **2**.



1 **2**

Compound	R″	Product	Yield (%)
1a (R′ = Ph)	*n*-Bu	**2a**	88
1a (R′ = Ph)	*i*-Pr	**2b**	84
1a (R′ = Ph)	$PhCH_2$	**2c**	76
1a (R′ = Ph)	*t*-Bu	**2d**	58
1e (R′ = *i*-Pr)	$Ph(CH_2)_3$	**2e**	84
1f (R′ = *n*-Pr)	$Ph(CH_2)_3$	**2f**	82
1g (R′ = *p*-NO_2–Ph)	*n*-Bu	**2g**	89
1h (R′ = *m*-NO_2–Ph)	*n*-Bu	**2h**	94
1i (R′ = *p*-Cl–Ph)	*n*-Bu	**2i**	80
1j (R′ = *p*-MeO–Ph)	*n*-Bu	**2j**	79

Note: Reaction conditions: at room temperature over 1.5 days.

all generated the desired product in good yield, but a sterically hindered alcohol such as *t*-BuOH may result in a lower yield.

Afterwards, we used a primary alcohol ($Ph(CH_2)_3OH$) as a nucleophile to react with two types of aliphatic aldehydes (**1e** and **1f**). These two aliphatic aldehydes have different degrees of steric hindrance adjacent to their respective carbonyl groups, but they both worked well and similarly in the peroxyacetal synthesis.

We further explored electronic effects on this peroxyacetal synthesis. We used various substituted benzaldehydes as an aldehyde substrate to react with *n*-BuOH. The substituent includes *p*-NO_2, *m*-NO_2, *p*-Cl, and *p*-MeO, ranging from highly electron-withdrawing to highly electron-donating. What we found was that benzaldehyde with a highly electron-withdrawing substituent gave the peroxyacetal very easily and in high yield. Just like the synthesis of the other peroxyacetals mentioned above, they worked very well without using a dehydrating agent such as 4 Å molecular sieves. However, when we carried out the peroxyacetal synthesis for an aromatic aldehyde substrate with a strong electron-donating substituent such as *p*-MeO, conversion to the peroxyacetal was very low (<10%). This low conversion was significantly improved by using a very dry solvent and activated 4 Å molecular sieves.

In the $TiCl_4$-promoted nucleophilic addition of both TBHP and an alcohol to an aldehyde, we usually had acetal and bisperoxyacetal as by-products. When the ratio of the quantities for aldehyde, alcohol, and TBHP was 1:1:1 in the peroxyacetal synthesis, we obtained little of the acetal by-product. When the ratio was 1:1:2, we obtained little of the bisperoxyacetal. The best ratio for these substances was 1:1:1.7, where the major product was peroxyacetal with negligible acetal and bisperoxyacetal by-products.

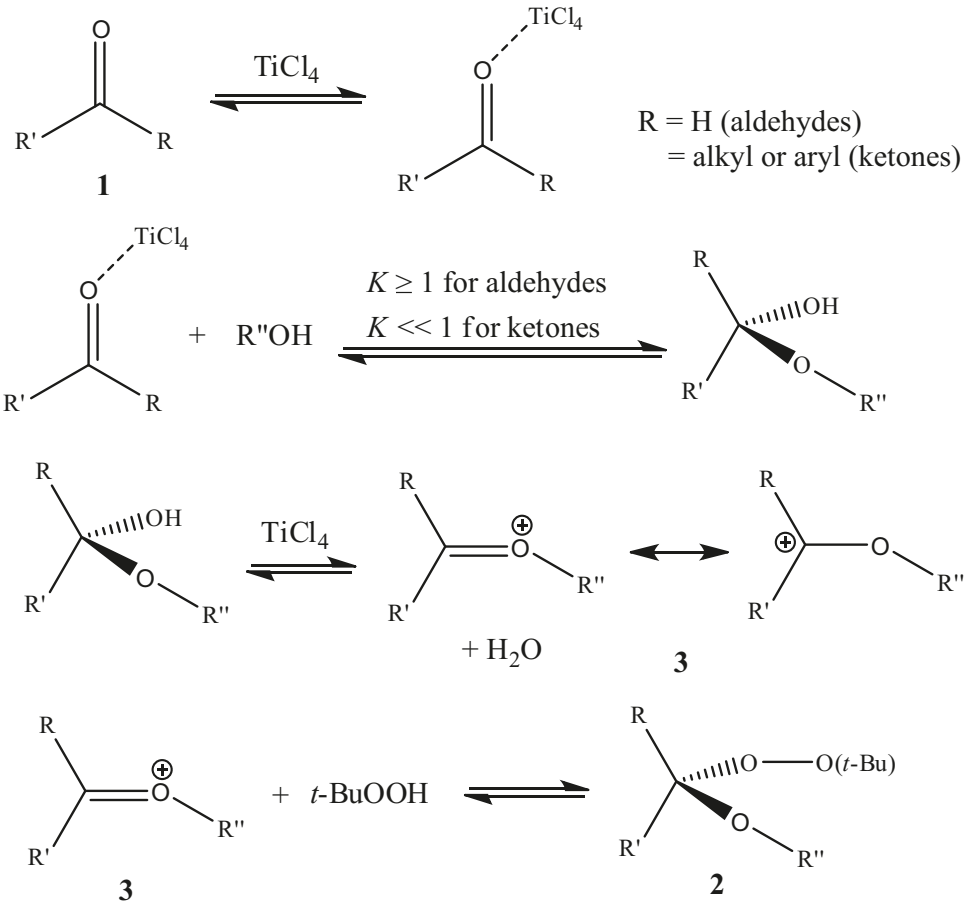
The limitation for the $TiCl_4$-promoted peroxyacetal synthesis is that the substrate cannot be a ketone. The ketone substrates we tried included acetone, acetaphenone, benzophenone, and benzil. This methodology did not work out for all the ketones even under very dry conditions and with a dehydration agent. This is quite different from ketal synthesis and that inspired us to analyze the reaction mechanism for the $TiCl_4$-promoted peroxyacetal synthesis.

Advantages of the $TiCl_4$-promoted peroxyacetal synthesis are as follows: (*i*) The method can be carried out at room temperature; (*ii*) Most peroxyacetal syntheses do not need a dehydrating agent and still achieve high yields, except for aldehyde substrates with highly electron-donating substituents. For aldehyde substrates with highly electron-donating substituents, one can still obtain peroxyacetals in high yield as long as a dried solvent and dehydrating agent are used; (*iii*) The peroxyacetal synthesis is selective for aldehyde substrates in the presence of ketone groups; (*iv*) It is unnecessary to convert aldehydes into acetals or vinyl ethers before preparation of peroxyacetals.

The mechanism for the $TiCl_4$-promoted peroxyacetal synthesis from an aldehyde substrate is assumed to be similar to that for acid-catalyzed acetal synthesis from an aldehyde substrate. Acid-catalyzed acetal synthesis from an aldehyde substrate usually involves two parts: (*i*) formation of hemiacetal from aldehyde and (*ii*) formation of acetal from hemiacetal. Then, the mechanism for the $TiCl_4$-promoted peroxyacetal synthesis from an aldehyde substrate is assumed to involve the same two parts (shown in Scheme 1). Chemists paid more attention to each of the two parts of the mechanism separately rather than the whole integrated mechanism.[9] In this paper, we will not only investigate each part of the mechanism, but also analyze the integrated mechanism as a whole.

For the second part of the mechanism, a hemiacetal intermediate may eliminate the OH group with the assistance of $TiCl_4$ activation,[10] forming a trigonal carbon and stabilized carbocation **3**. This ion will react very fast with an alcohol or TBHP to yield an acetal or ketal. The carbocation **3** is better stabilized by alkyl or aryl group than by H. If the formation of carbocation **3** is rate-limiting in the $TiCl_4$-promoted peroxyacetal synthesis, the activation energy for the formation of peroxyketal is supposed to be smaller than that for the formation of peroxyacetal. Therefore, we should have been

Scheme 1. Proposed mechanism for $TiCl_4$-promoted peroxyacetal synthesis.



able to prepare peroxyketal with this method, but we could not. This indicates that the second part of the mechanism (formation of acetal from hemiacetal) does not play the most important role in the $TiCl_4$-promoted peroxyacetal synthesis, but the first part of the mechanism (formation of hemiacetal from aldehyde) does.

The first part of the mechanism (formation of the hemiacetal or hemiketal) is similar to that for aldehyde or ketone hydration. Aldehyde hydration is usually thermodynamically favorable with an equilibrium constant close to or greater than 1, but ketone hydration is thermodynamically unfavorable with an equilibrium constant much smaller than 1. There are two pieces of evidence that support that the first part of the mechanism (formation of hemiacetal from aldehyde) plays the most important role in the $TiCl_4$-promoted peroxyacetal synthesis. The first piece of evidence is that peroxyketals cannot be prepared by this method. The possible explanation is that the thermodynamically unfavorable formation of hemiketal makes the formation of peroxyketal impossible in the $TiCl_4$-promoted peroxyacetal synthesis. The second piece of evidence is that the conversion to **2j** in the absence of a drying agent is much lower than the conversion to **2g** or **2h** under the same conditions. The possible explanation is that a strong electron-donating group (*p*-MeO) on **1j** and **2j** makes the formation of hemiacetal less thermodynamically favorable than a strong electron-withdrawing group (NO_2) and this causes the formation of peroxyacetal at low conversion levels. We solved the low-conversion problem by removing the water by-product with 4 Å molecular sieves, shifting the equilibrium position to the peroxyacetal product. This is usually found in the acetal synthesis, where azeotropic distillation is usually used as a way to remove the water by-product. However, azeotropic distillation is not a suitable way to remove water in the peroxyacetal synthesis because heat may further degrade the peroxyacetal product. Hence, the reason why the peroxyacetal synthesis does not work with ketones is that the formation constants from the ketones to the corresponding hemiketals in the first part of the reaction are too small to generate a large enough concentration of hemiketals for the second part of the reaction.

Conclusion

$TiCl_4$-promoted nucleophilic addition of both TBHP and an alcohol to an aldehyde generated a peroxyacetal. This methodology works selectively for aldehydes, but not for ketones. Various alcohols and aldehydes can be used in this peroxyacetal synthesis. To reduce the acetal and bisperoxyacetal by-products to a negligible amount, the best ratio of the quantities for aldehyde, alcohol, and TBHP in the peroxyacetal synthesis is 1:1:1.7. The equilibrium constant for the formation of hemiacetal plays the most important role in the $TiCl_4$-promoted peroxyacetal synthesis. The larger the formation constant of hemiacetal, the better conversion the peroxyacetal synthesis can reach.

Experimental section

General procedure for synthesis of peroxyacetals (2)

To aldehyde (1 mmol) and 4 Å molecular sieves (0.5 g) in $CHCl_3$ or $CDCl_3$ (2 mL) at room temperature was added $TiCl_4$ (0.1 mmol, 10% in $CHCl_3$ or $CDCl_3$). The mixture was stirred at room temperature for 1 h. Toluene solutions of TBHP (1.7 mmol) and alcohol (1 mmol) were added into the mixture, followed by stirring at room temperature for around 1–2 days. The reaction was monitored by ^{1}H NMR spectrometry until the reaction was complete. The product **2** was purified by column chromatography with silica gel as a stationary phase and hexane/EtOAc as a mobile phase.

(*tert*-Butylperoxybutoxymethyl)benzene (2a)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.49 (m, 5H), 5.84 (s, 1H), 3.99 (dt, J = 9.6, 6.5 Hz, 1H), 3.67 (dt, J = 9.6, 6.7 Hz, 1H), 1.66 (m, 2H), 1.42 (m, 2H), 1.30 (s, 9H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.9, 128.7, 128.1, 126.9, 106.0, 80.7, 69.3, 32.0, 26.5, 19.3, 13.8. The NMR data were in agreement with those previously reported for this compound (ref. 11). Anal. calcd for $C_{15}H_{24}O_3$: C 71.38, H 9.59; found: C 71.41, H 9.57.

(*tert*-Butylperoxyisopropoxymethyl)benzene (2b)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16–7.34 (m, 5H), 5.73 (s, 1H), 4.04 (m, 1 H), 1.17 (d, J = 6.1 Hz, 3H), 1.12 (s, 9H), 1.05 (d, J = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.5, 128.6, 128.1, 126.9, 104.4, 80.6, 71.5, 26.5, 23.0, 22.5. Anal. calcd for $C_{14}H_{22}O_3$: C 70.54, H 9.31; found: C 70.52, H 9.33.

(Benzyloxy-*tert*-butylperoxymethyl)benzene (2c)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27–7.52 (m, 5H), 5.97 (s, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.88 (d, J = 12.3 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.2, 136.5, 128.8, 128.3, 128.2, 127.7, 127.5, 126.9, 105.1, 81.0, 70.9, 26.5. Anal. calcd for $C_{18}H_{22}O_3$: C 75.48, H 7.75; found: C 75.50, H 7.72.

(*tert*-Butoxy-*tert*-butylperoxymethyl)benzene (2d)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32–7.49 (m, 5H), 5.96 (s, 1H), 1.30 (s, 9H), 1.26 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.8, 128.5, 128.0, 127.1, 100.4, 80.4, 74.7, 28.8, 26.6. Anal. calcd for $C_{15}H_{24}O_3$: C 71.38, H 9.59; found: C 71.36, H 9.63.

(3-(1-*tert*-Butylperoxy-2-methylpropoxy)propyl)benzene (2e)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09–7.22 (m, 5H), 4.47 (d, J = 6.1 Hz, 1H), 3.90 (m, 1H), 3.49 (m, 1H), 2.64 (t, J = 6.9 Hz, 2H), 1.85 (m, 2H and 3H), 1.17 (s, 9H), 0.90 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.2, 128.4, 128.2, 125.6, 110.4, 80.2, 69.5, 32.4, 31.7, 31.5, 26.5, 18.2, 17.9. Anal. calcd for $C_{17}H_{28}O_3$: C 72.80, H 10.07; found: C 72.83, H 10.04.

(3-(1-*tert*-Butylperoxybutoxy)propyl)benzene (2f)

Colorless oil. ^{1}H NMR (300 Hz, $CDCl_3$) δ: 7.21–7.33 (m, 5H), 4.90 (t, J = 5.6 Hz, 1H), 3.99 (m, 1H), 3.62 (m, 1H), 2.76 (t, J = 7.9, 2H), 1.98 (m, 2H), 1.69 (m, 2H), 1.49 (m, 2H), 1.29 (s, 9H), 0.99 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.0, 128.4, 128.1, 125.6, 106.4, 80.0, 68.4, 34.4, 32.3, 31.5, 26.4, 18.2, 13.9. Anal. calcd for $C_{17}H_{28}O_3$: C 72.80, H 10.07; found: C 72.84, H 10.09.

1-(*tert*-Butylperoxybutoxymethyl)-4-nitrobenzene (2g)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.1 Hz, 2H), 5.85 (s, 1H), 4.05 (m, 1H), 3.71 (m, 1H), 1.65 (m, 2H), 1.46 (m, 2H), 1.25 (s, 9H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.0, 143.8, 127.9, 123.3, 104.2, 81.0, 68.8, 31.8, 26.4, 19.2, 13.8. Anal. calcd for $C_{15}H_{23}NO_5$: C 60.57, H 7.80, N 4.71; found: C 60.54, H 7.81, N 4.70.

1-(*tert*-Butylperoxybutoxymethyl)-3-nitrobenzene (2h)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.34 (s, 1H), 8.20 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 5.86 (s, 1H), 4.06 (m, 1H), 3.72 (m, 1H), 1.69 (m, 2H), 1.47 (m, 2H), 1.39 (s, 9H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.1, 139.2, 133.0, 129.0, 123.5, 122.2, 104.1, 81.0, 69.8, 31.8, 26.4, 19.2, 13.8. Anal. calcd for $C_{15}H_{23}NO_5$: C 60.57, H 7.80, N 4.71; found: C 60.56, H 7.84, N 4.72.

1-(*tert*-Butylperoxybutoxymethyl)-4-chlorobenzene (2i)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 5.78 (s, 1H), 3.95 (m, 1H), 3.67 (m, 1H), 1.66 (m, 2H), 1.43 (m, 2H), 1.27 (s, 9H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.4, 134.1, 128.3, 128.2, 105.1, 80.8. 69.4, 31.1, 26.5, 19.4, 13.8. Anal. calcd for $C_{15}H_{23}ClO_3$: C 62.91, H 8.10; found: C 62.89, H 8.12.

1-(*tert*-Butylperoxybutoxymethyl)-4-methoxybenzene (2j)

Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.78 (s, 1H), 3.93 (m, 1H), 3.81 (s, 3H), 3.65 (m, 1H), 1.65 (m, 2H), 1.44 (m, 2H), 1.28 (s, 9H), 0.94 (t, J = 0.72 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.8, 128.1, 114.2, 113.5, 105.9, 80.5, 69.2, 55.2, 32.0, 26.5, 19.3, 13.8. Anal. calcd for $C_{16}H_{26}O_4$: C 68.04, H 9.29; found: C 68.07, H 9.27.

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